

REMARKS

Entry of the foregoing and favorable reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. Section 1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendment, Claims 1, 5, 6 and 8 have been amended to correct typographical or grammatical errors. Claims 25 and 26 have been added. Applicants submit that Claim 25 is the combination of Claim 1 and parts of Claim 3, as is Claim 26 with a minor modification. Therefore, no new search should be required by the Examiner. Applicants submit that no new matter has been added via this amendment.

Claims 1 to 8 have been rejected under 35 U.S.C. §103 (a) as being unpatentable over Haicheur et al in view of Wang et al. For the following reasons, this rejection is respectfully traversed.

Haicheur et al disclose that the B subunit of Shiga Toxin fused to a tumor peptide derived from the mouse mastocytoma p815 induces the generation of peptide-specific CTL in mice. The peptides, which were fused to the B subunit of Shiga toxin were synthetic peptides SIINFEKL, encompassing the 257-264 residues of OVA and LPYLGWLVF, encompassing the 35-43 residues of P1A. Thus the peptides which were fused to the B subunit of Shiga toxin were eight and nine amino acids in length, respectively.

Haicheur et al also disclose that these fusion proteins elicit CTL and target dendritic cells to allow MHC Class I-restricted pathway presentation. This reference fails to disclose or suggest using a cysteine residue coupled to the C-terminus of the Shiga toxin B subunit. Moreover, this reference fails to disclose or suggest that proteins can be coupled to this universal carrier and the Gb3 receptor function maintains its binding capacity.

Wang et al disclose structured synthetic antigen libraries (hereinafter SSAL) composed of related peptides synthesized simultaneously in a single peptide synthesis. These peptides can be used in diagnosis or as vaccines. The overall length of the SSAL's can range from 8 to about 100 amino acids. This reference also discloses that extra residues such as KKK can be added at the amino terminus to increase peptide solubility and cysteine can be added to facilitate coupling to carrier molecules. The carrier molecules are described as bovine serum albumin, human serum albumin, red blood cells or latex particles.

A person skilled in the art when faced with the disclosure of Wang et al would realize that the carrier molecules described therein are used to augment the immunogenicity of the small peptides. Indeed, it was known in the art that low molecular molecules such as peptides are often not sufficiently immunogenic to elicit an immune response alone. Synthetic peptides which are used to generate antibodies can be made immunogenic by conjugation to a suitable carrier such as BSA, HSA etc. Therefore the carriers described in Wang et al are not considered carriers that enter a particular pathway in the cell or bind to cell receptors. This is clear from the teachings at pages 23-24 of this reference where the following is stated:

Based on the immunoreactivities of the SSALs, they are useful in a vaccine composition to treat or prevent the infection caused by the infectious agent from which they are derived. These vaccine compositions containing one or more SSALs, alone or when coupled to a carrier or polymerized to homo- or hetero-dimers or higher oligomers by cysteine oxidation, by induced disulfide cross-linking, or by use of homo- or hetero-functional multivalent cross-linking reagents, can be introduced into normal subjects to stimulate production of antibodies.

Thus, the carriers described in Wang et al do not have to maintain a functional structure in order to be active.

Moreover, even if a skilled artisan would add additional amino acids as spacers between the carrier and the peptide such as KKK, when applied to the disclosure of Haicheur et al; i.e., to the B subunit of Shiga toxin, the construct would not be active. This is taught and claimed in the present invention since Z is 0 or 1. At page 3 of the specification it is clearly stated that if the Z linker is too long; i.e., ≥ 2 the construct does not function, due to the loss of binding to the Gb3 or the binding of the molecule of interest.

Indeed, the skilled artisan would take into consideration that for the Shiga B subunit to maintain its function as binding to the Gb3 receptor, its correct conformational structure has to be maintained. It was known at the time of filing of the present application that for plasma membrane binding and internalization requires a noncovalent interaction with the B subunit of Shiga toxin. The B fragment of Shiga toxin's structure is a pentamer in which the central axis is lined by α -helices from the monomers. These helices interact with each other through antiparallel β -sheets to form a ring-like structure, which has to be maintained for receptor binding.

Furthermore, the person skilled in the art would realize that for the Shiga B toxin to bind to the Gb3 receptor on specific cells, such as dendritic cells, it must contain a specific combination of atoms that represents the correct size, geometric shape and charge in order to interact and bind.

The specific size, geometric shape and charge can be influenced by what is attached to the C and N terminals of the construct of the Shiga B toxin. It was known in the art, as disclosed by Haicheur et al that peptides fused to the C terminal end having eight and nine amino acids, that the binding to Gb3 was maintained. These sequences are limited in length and hence it is not unexpected that Gb3 binding activity is maintained.

Moreover, the amino acid sequences of the peptides fused to the Shiga B toxin described in Haicheur et al did not contain a single cysteine. Hence, there is simply no teaching or suggestion in Haicheur et al that a construct containing a cysteine at the end of the C-terminal of Shiga B toxin would in fact retain Gb3 binding ability. Indeed it is well known in the art that cysteine residues often form disulfide bridges and these bridges can influence ligand binding properties.

Applicants submit that the combination of these references fails to render the present invention obvious since the skilled artisan would not have any expectation of success that adding a C-terminal cysteine, as well as a molecule attached to the cysteine, to the Shiga B toxin, that such a construct would in fact maintain its size, geometric shape and charge such that its binding capacity to Gb3 is maintained. Applicants submit that there would be simply no expectation of success.

As stated in *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.* 68 F. Supp 2d 508, 534, 535 (D.N.J. 1999), *later opinion*, 166 F. Supp 2d 19 (D.N.J. 2001) *aff'd* 320 F.3d 1339, 65 USPQ2d 1961 (Fed. Cir. 2003).

The case law is unambiguous that an invention is not unpatentable merely because it was obvious to try...An invention is merely obvious to try when the results suggested by the prior art do not create a reasonable expectation of success...In the obvious to try situation, the prior art gives either no indication of which parameters are critical or no direction as to which of many possible choices is likely to succeed.

No specific parameters were in fact given as to whether a cysteine at the C terminal end of the Shiga B toxin, the cysteine further being coupled to a molecule would in fact retain Gb3 receptor activity. Moreover, there is no guidance given in either reference of the amount of extra

residues or which residues could be attached to the C-terminal of the Shiga toxin B subunit such that ligand binding activity is maintained. Wang et al does not provide any guidance concerning what type of additional amino acids should be avoided; i.e., those with sulphydryl groups, as disclosed in the present invention. This latter fact is not surprising since conformational structure of the carrier molecule does not have to be maintained in Wang et al.

Lacking proper guidance in both cited prior art references, Applicants submit that the presently claimed invention is not obvious in view of the combination thereof.

Finally, Applicants submit that it was demonstrated in the present specification that coupling to the universal carrier of whole proteins, as well as complex protein mixtures following the procedure set forth in the specification, while retaining Gb3 binding activity is feasible. This is quite an unexpected result especially in view of the size of the protein; i.e., chicken ovalbumin has 385 amino acid residues. Hence, at least claims 25 and 26 are not obvious in view of the cited prior art.

In conclusion, Applicants submit that the presently claimed invention is not obvious over Haicheur et al in view of Wang et al for the reasons set forth above.

Thus, withdrawal of this rejection is respectfully requested.

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

If the Examiner has any questions concerning this application, the Examiner is requested to contact MaryAnne Armstrong, Reg. No. 40,069 at the telephone number of (703) 205-8000.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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